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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/044,696	03/18/1998	GAIL BARCHFELD	1393.002	8826

27476 7590 10/22/2002

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EXAMINER

DEVI, SARVAMANGALA J N

ART UNIT PAPER NUMBER

1645

DATE MAILED: 10/22/2002

34

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/044,696

Applicant(s)

Barchfeld et al.

Examiner

S. Devi, Ph.D.

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Apr 22, 2002.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19, 21, and 25-30 ~~is/are~~ pending in the application.
- 4a) Of the above, claim(s) 1-18 ~~is/are~~ withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19, 21, and 25-30 ~~is/are~~ rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other: _____

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DETAILED ACTION

Request for Continued Examination

1) A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicants' submission filed on 04/22/02 (paper no. 28) has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 04/22/02 (paper no. 29) in response to the Final Office Action mailed 10/24/01 (paper no. 24). With this, Applicants have amended the specification.

Sequence Listing

3) Acknowledgment is made of Applicants' raw sequence listing filed 07/16/02 (paper no. 32).

Status of Claims

4) Claim 19 has been amended via the amendment filed 04/22/02.
Claims 23 and 24 have been canceled via the amendment filed 04/22/02.
Claims 1-19, 21 and 25-30 are pending in this application.
Claims 19, 21 and 25-30 are under examination.

Prior Citation of Title 35 Sections

5) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

6) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection Maintained

7) The objection to the drawings made under 37 C.F.R. 1.84 in paragraph 7 of the Office

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Action mailed 08/04/99 (paper no. 10) and maintained in paragraph 4 of the Office Action mailed 04/25/00 (paper no. 15) is still maintained for reasons set forth therein. Applicants are asked to note the changes effected 03 May 2001, particularly the changes to the 'Timing of Corrections':

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85; 1097 O.G. 36

New formal drawings must be filed with the changes incorporated therein. The art unit number, application number (including series code) and number of drawing sheets should be written on the reverse side of the drawings. Applicant may delay filing of the new drawings until receipt of the "Notice of Allowability" (PTOL-37 or PTO-37). If delayed, the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability" to avoid extension of time fees. Extensions of time may be obtained under the provisions of 37 C.F.R. 1.136(a) for filing the corrected drawings (but not for payment of the issue fee). The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the three month shortened statutory period set in the "Notice of Allowability" (PTO-37). Within that three month period, two weeks should be allowed for review of the new drawings by the Office. If a correction is determined to be unacceptable by the Office, Applicant must arrange to have an acceptable correction re-submitted within the original three month period to avoid the necessity of obtaining an extension of time with extension fees. Therefore, applicant

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should file corrected drawings as soon as possible.

Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

Specification - New Matter

8) The amendment filed 04/22/02 (paper no. 29) is objected to under 35 U.S.C. § 132, because it introduces new matter into the disclosure. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows. On page 6, line 3, Applicants have added the sentence: "Figure 3 (SEQ ID NO: 5) shows the amino acid sequence of a wild-type LT-A". Additional figure, Figure 3 depicting an amino acid sequence, has been added to the specification. The raw Sequence Listing now included SEQ ID NO: 5. Applicants point to the last paragraph beginning on page 3 of the specification as indicating that "CT and LT are generally interchangeable, showing considerable homology". However, this part of the instant specification does not provide descriptive support for the added limitations, SEQ ID NO: 5 and Figure 3.

Applicants are required to cancel the new matter in the response to this Office Action.

Rejection(s) Moot

9) The rejection of claim 23 made in paragraph 14 of the Office Action mailed 01/12/01 (paper no. 19) and maintained in paragraph 8 of the Office Action mailed 10/24/01 (paper no. 24) under 35 U.S.C. § 102(e) as being anticipated by Domenighini *et al.* (US 6,149,919 with an effective filing date of 12/30/1992) ('919) as evidenced by Tommaso *et al.* (*Infect. Immun.* 64: 974-979, 27 February 1996, already of record) or Partidos *et al.* (*Immunology* 89: 483-487, December 1996, already of record), is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

10) The rejection of claims 19, 21 and 25-27 made in paragraph 14 of the Office Action mailed 01/12/01 (paper no. 19) and maintained in paragraph 8 of the Office Action mailed 10/24/01 (paper no. 24) under 35 U.S.C. § 102(e) as being anticipated by Domenighini *et al.* (US 6,149,919 with an effective filing date of 12/30/1992) ('919) as evidenced by Tommaso *et al.* (*Infect. Immun.* 64: 974-979, 27 February 1996, already of record) or Partidos *et al.* (*Immunology* 89: 483-487, December 1996, already of record), is withdrawn in light of

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Applicants' amendments to the base claim.

11) The rejection of claims 28-30 made in paragraph 15 of the Office Action mailed 01/12/01 (paper no. 19) and maintained in paragraph 10 of the Office Action mailed 10/24/01 (paper no. 24) under 35 U.S.C. § 103(a) as being unpatentable over Domenighini *et al.* (US 6,149,919) as applied to claim 19 above, and further in view of Rappuoli *et al.* (WO 95/17211, published 06/29/95 -Applicants' IDS) (WO '211), is withdrawn in light of Applicants' amendments to the base claim.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

12) Claims 19, 21 and 25-30 rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method for immunizing a vertebrate subject comprising parenterally administering an effective amount of a mutant of the bacterial ADP-ribosylating toxin, LT-R72, and at least one selected antigen, does not reasonably provide enablement for such a method using the mutant LT-R72, that is **detoxified**, as instantly claimed.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, although the construction and evaluation as an adjuvant of LT-R72 is described in the specification, the state of the art suggests that an LT mutant having a site directed substitution of Alanine to Arginine at position 72 is not "detoxified" as claimed currently. For instance, Pizza *et al.* (*Mol. Microbiol.* 14: 51-60, October 1994, already of record) taught such a mutant. See Table 1, Fig 1k and page 57, left column, last paragraph. Table 1 illustrates that the mutant named "R72" having a Ala->Arg sub A mutation remained toxic (toxicity is rated as ++). Pizza *et al.* stated that this mutant was "fully toxic" as in the case of the mutant having a substitution at Ser-68 (see page 57, left column, last paragraph). Similarly, Figures 4 and 5 of the

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WO 98/18928 patent (already of record) clearly show that LT-R72 mutant is not “detoxified”, while LT-K63 is. Furthermore, this patent on page 44, lines 16-21, explicitly stated that LT-A72R was “less toxic” whereas LTK63 was “completely non-toxic”. Clearly, LT-R72 is not detoxified as claimed in the instant base claim 19. Absent a showing that the LT-R72 is ‘detoxified’ contrary to what the state of the art reflects, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed due to the lack of specific disclosure and guidance, the lack of working examples enabling a ‘detoxified’ LT-R72, and the quantity of experimentation necessary.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

13) Claims 19, 21 and 25-30 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 19 is confusing and/or redundant in the recitation “**toxin** ADP-ribosylating **toxin**” (see lines 4 and 5) [Emphasis added].

(b) Claims 21 and 25-30, which depend directly or indirectly from claim 19, are also rejected as being indefinite because of the indefiniteness or vagueness identified above in the base claim.

Remarks

14) Claims 19 and 21-27 stand rejected.

15) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center’s telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

16) Any inquiry concerning this communication or earlier communication(s) from the

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Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

October, 2002


S. DEVI, PH.D.
PRIMARY EXAMINER